# Comparative study of vaginal danazol vs diphereline (a synthetic GnRH agonist) in the control of bleeding during hysteroscopic myomectomy in women with abnormal uterine bleeding: a randomized controlled clinical trial

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## ABSTRACT

*Objective:* To compare the usefulness of vaginal danazol and diphereline in the management of intra-operative bleeding during hysteroscopy.
*Design:* Randomized controlled clinical trial.
*Setting:* University hospital.
*Patients:* One hundred and ninety participants of reproductive age were enrolled for operative hysteroscopy. Thirty women were excluded from the study.
*Interventions:* One hundred and sixty participants with submucous myomas were allocated at random to receive either vaginal danazol (200 mg BID, 30 days before surgery) or intramuscular diphereline (twice with a 28-day interval).
*Main outcome measures:* Severity of intra-operative bleeding, clarity of the visual field, volume of media, operative time, success rate for completion of operation and postoperative complications.
*Results:* Overall, 145 patients completed the study. In the danazol group, 78.1% of patients experienced no intra-operative uterine bleeding, and 21.9% experienced mild bleeding. In the diphereline group, 19.4% of patients experienced no intra-operative uterine bleeding, but mild, moderate and severe bleeding was observed in 31.9%, 45.8% and 2.8% of patients, respectively. The difference between the groups was significant ($p < 0.001$). A clear visual field was reported more frequently in the danazol group compared with the diphereline group (98.6% vs 29.2%, $p < 0.001$). The mean operative time was 10.9 min and 10.6 min in the danazol and diphereline groups, respectively ($p = 0.79$). The mean volume of infused media was 2.0l in both groups ($p = 0.99$). The success rate was 100% for both groups with no intra-operative complications.
*Conclusion:* Both vaginal danazol and diphereline were effective in controlling uterine bleeding during operative hysteroscopy. However, vaginal danazol provided a clearer visual field.

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## Introduction

Abnormal uterine bleeding is a significant issue, often caused by uterine fibroids [1]. Hysteroscopy can be used for visualizing and treating intra-uterine benign focal lesions. This operative technique is best performed with a flat and/or atrophic endometrium [2]. Complete myoma resection is one of the main determinants of treatment success. However, hysteroscopy may not be successful due to continuous uterine bleeding. Endometrial thickness or intra-uterine pathologies may further narrow the already-limited space, and obscure the vision in ways that are not safe and acceptable for the procedure. Any effort to enhance the feasibility of hysteroscopy will increase its success rate. Different pharmaceutical compositions are used before surgery to reduce the thickness of the endometrium in order to improve visibility during surgery, such as gonadotropin-releasing hormone (GnRH) agonists [3] and other anti-estrogenic compounds such as cabergoline [4], raloxifene plus progestins [5], ulipristal acetate [6] and gestrinone

[7]. Although GnRH agonists have been used to reduce the size of uterine fibroids and to prepare the uterine cavity for hysteroscopic resection, the advantages of their use are still being questioned [8].

More recently, danazol has been administered for the treatment of endometrial hyperplasia with satisfactory results [9]. Danazol treatment, along with expression of hypoestrogenism through inhibition of the hypothalamic-pituitary axis, decreases aromatase expression with a direct, albeit dose-dependent, effect on the endometrium [10]. In cases of "minor" hysteroscopic surgery (e.g., removal of intracavitary fibroids), GnRH agonists may be considered too expensive and seen as "overtreatment". In such cases, danazol, which is less expensive with a shorter treatment course for pre-operative endometrial preparation, may be considered to be more suitable and sufficient to obtain satisfactory results and a better surgical environment. Danazol is also capable of reducing uterine volume, menorrhagia, endometrial thickness and length of surgery [10].

This randomized controlled clinical trial was designed to assess the short-term intra- and postoperative outcomes and consequent quality of treatment when using vaginal danazol before hysteroscopic surgery compared with GnRH agonists.

## Materials and methods

This randomized controlled clinical trial was conducted from August 2013 to January 2015 at Alzahra Teaching Hospital, Tabriz University of Medical Sciences. One hundred and ninety participants of reproductive age with a history of persistent mild-to-moderate uterine bleeding that was resistant to treatment, and submucous myomas <4 cm in diameter as the underlying cause of bleeding were enrolled. One hundred and sixty of these women were eligible for hysteroscopic resection of the myoma. The researchers received ethical approval from the University Ethical Committee and the patients' informed consent was obtained. Pilot study data indicated that 29% of patients in the diphereline group experienced no intra-operative uterine bleeding, and 52% of patients experienced no intra-operative uterine bleeding in the danazol group. Thus, our study required 72 experimental subjects and 72 control subjects in order to reject the null hypothesis that the intra-operative uterine bleeding experience rates for experimental and control subjects are equal with a power of 0.8. The Type I error probability associated with the test of the null hypothesis is 0.05. In order to reject the null hypothesis, then, each group had a sample size of 80. Random sampling was used to assign the patients to groups. Randomization was performed using Rand List Version 2.1 (DatInf GmbH, Tübingen, Germany) with sequentially-numbered containers. Research coworkers introduced the eligible patients to the main researcher who generated the random allocation sequence, enrolled the participants and assigned participants to interventions. Pap smear, transabdominal and transvaginal sonography and official endometrial sampling were all undertaken to determine the pathology of the endometrium before pharmaceutical treatment. Patients with hypertension; liver problems; adnexal pathology; lung, renal, cardiovascular and metabolic diseases; cervical and uterine cancer; submucous myomas >4 cm in diameter; uterine septa; genital tract infections; pregnancy and recent history of anticoagulant consumption were excluded. Eligible patients were divided at random into two equal groups. One group received vaginal danazol (200 mg BID) (Cipla Ltd, Mumbai Central, Mumbai, India), which was placed into the posterior vaginal fornix every 12 h for 30 days prior to hysteroscopy (starting on the first day of menstrual bleeding), and the other group received diphereline (3.75 mg/im) (IPSEN Pharma Biotec, Paris, France) every 28 days for 2 months prior to hysteroscopy, starting on the 18th day of the menstrual cycle. The amount of bleeding during surgery was determined using an ordinal scale. During surgery, the amount of bleeding was classified from zero (no bleeding) to 5 (severe bleeding) by agreement between the surgeon and nurse. In addition to routine blood tests, sodium and potassium levels were measured before surgery and 6 h after surgery. Changes in blood pressure and heart rate during anaesthesia were documented. Dextrose 5% was used as a medium in both groups. Care providers and those assessing the outcomes were blinded after assigning the patients to the interventions. All patients underwent general anaesthesia in the same way, and the same surgeon performed all procedures.

### Statistical analysis

Data are expressed as mean ± standard deviation (SD) and frequency (%). Statistical Package for the Social Sciences Version 16 (SPSS Inc., Armonk, NY, USA) was used to analyze the data. Normally distributed quantitative data were studied using a Kolmogorov–Smirnov test and a $q$–$q$ plot. A $t$-test was used for independent samples to compare quantitative variables. Qualitative data between the two groups were compared using Chi-squared test or Fisher's exact test, and $p < 0.05$ was considered to indicate statistical significance. In terms of length of disease, the standard error of the mean has been reported rather than the SD.

## Results

One hundred and forty-five patients (73 patients in the danazol group and 72 patients in the diphereline group) completed the study. The CONSORT flow diagram is shown in Appendix A, and the characteristics of the patients are summarized in Table 1. Details of intra-operative bleeding and intra-uterine view in the two groups are shown in Table 2; the differences between the two groups were statistically significant ($p < 0.001$). The results of pre-operative partial thromboplastin time (PTT) in the danazol and diphereline groups were 30.5 ± 2.2 and 32.2 ± 3.2, respectively; this difference was significant ($p < 0.001$). The results show that postoperative serum haematocrit and haemoglobin levels were significantly lower in the diphereline group compared with the danazol group [2.5% vs 1.3% ($p = 0.01$) and 0.9 vs 0.3 mg/dl ($p < 0.001$), respectively]. The mean serum volume used during surgery in the danazol and diphereline groups was 2.0 ± 1.2 l and 2.0 ± 1.4 l, respectively

**Table 1**
The characteristics of the studied patients; group 1 (danazol) and group 2 (diphereline).

| Variable | Group 1 ($n$ = 73) Mean ± SD | Group 2 ($n$ = 72) Mean ± SD | $p$-value[*] |
|---|---|---|---|
| Age | 40.22 ± 5.12 | 39.50 ± 5.25 | 0.14 |
| Gravidity | 3.05 ± 1.54 | 4.14 ± 1.71 | 0.76 |
| Parity | 2.58 ± 1.33 | 2.72 ± 1.79 | 0.56 |
| Length of disease (months) | 32.04 ± 3.96 | 18.60 ± 2.52 | 0.01 |
| Number of myomas | 1.36 ± 0.59 | 1.25 ± 0.53 | 0.25 |

[*] Differences were considered statistically significant at $p < 0.05$.

**Table 2**
The percentage of intraoperative bleeding and view in group 1 (danazol) and group 2 (diphereline).

| Variable | Group 1 % ($N$) | Group 2 % ($N$) | $p$-value[*] |
|---|---|---|---|
| No bleeding | 78.1 (57) | 19.4 (14) | <0.001 |
| Mild bleeding | 21.9 (16) | 31.9 (23) | |
| Moderate bleeding | 0.0 | 45.8 (33) | |
| Severe bleeding | 0.0 | 2.8 (2) | |
| Light view | 98.6 (72) | 29.2 (21) | <0.001 |
| Dark view | 1.4 (1) | 70.8 (51) | |

[*] Differences were considered statistically significant at $p < 0.05$, $N$ = number.

($p$ = 0.99). There was no significant difference in the mean length of surgery between the danazol ($10.9 \pm 5.9$ min) and diphereline ($10.6 \pm 6.4$) groups ($p$ = 0.79). There were no anaesthetic complications in any of the patients in either group. Nausea was only reported in one case (1.4%) as a postoperative complication in the danazol group (Fisher's exact test, $p$ = 0.05). Surgery was completed successfully in all patients in both groups.

## Comments

Success of hysteroscopic surgical procedures is strongly dependent on constant surgical field visibility. Operative hysteroscopy is best performed with a thin endometrium because it is easier to remove the intra-uterine pathology. Thus, the operating time will be shortened and the need for distension media for inspection of the uterine cavity will be reduced. Some studies have shown that using danazol or GnRH agonists to reduce the thickness of the endometrium before operative hysteroscopy resulted in better intra-operative and short-term postoperative outcomes. According to Tan and Lethaby, GnRH agonists produce slightly more consistent endometrial thinning than danazol, although both achieve satisfactory results [11]. The present study compared the efficacy and complications of vaginal danazol and diphereline in women with uterine myomas who were candidates for hysteroscopy. The results show that vaginal danazol was superior to diphereline in terms of the amount of intra-operative bleeding and clarity of the field of visibility during hysteroscopy. In addition, oral danazol and GnRH agonists have both been used with high efficacy in the treatment of endometriosis [12]. Cobellis et al. showed that the use of local danazol (vaginal or intra-uterine) was very effective for the treatment of endometriosis, and related complications were negligible [13]. In agreement with the present results, Campo et al. evaluated the influence of GnRH analogues for resectoscopic myomectomy, and found a significantly longer surgical time in pretreated patients [14]. Although GnRH agonists are effective for this purpose, the total cost is significantly higher due to the high price of these drugs [15]. Previous studies have focused on the efficacy of oral danazol in presurgical preparation of the endometrium for hysteroscopy or uterine bleeding control [16]. Tinelli et al. studied 6 months of treatment with oral danazol (200 mg/daily) and diphereline (3.75 mg/month) in two different groups; the reported incidence of side effects associated with oral danazol was higher, so its tolerability was lower compared with diphereline [17]. In other studies, it has been shown that GnRH analogues and danazol are the best-known and most effective treatments for presurgical preparation of the endometrium to improve the performance of hysteroscopy [18]. Tan and Lethaby [11] studied the efficacy and side effects of GnRH agonists and oral danazol to reduce the thickness of the endometrium before surgery in women with uncontrollable uterine bleeding. According to these authors, the endometrial thickness was slightly thinner in the GnRH agonist group than the danazol group, although both were accompanied with a satisfactory result. Conducting the procedure was easy, bleeding was controlled more effectively, and there was high patient satisfaction. In contrast to the present study, which found no significant difference in the surgical time between groups, Tan and Lethaby found that surgical time was lower in the GnRH agonist group compared with the danazol group, and both GnRH agonists and oral danazol had side effects in a large number of patients [11]. Another study reported that GnRH agonists and oral danazol had similar efficacy in preparing patients for endometrial destruction to stop uterine bleeding [19]. In contrast, Rai et al. found no improvement in clinical outcome and patient satisfaction in patients treated medically with oral danazol, medroxyprogesterone acetate or nafarelin before hysteroscopic resection of the endometrium [20]. Accordingly, although oral danazol could significantly reduce or stop uterine bleeding, the high incidence of side effects (metabolic and non-metabolic) has limited its use for this purpose [9]. However, some previous studies have reported good outcomes for vaginal danazol with few and insignificant systemic side effects [13,21]. Florio et al. compared the usefulness of vaginal danazol as a pre-operative preparation for hysteroscopic surgery with oral danazol. The patients who received vaginal danazol had significantly more hypotrophic endometrium, a shorter operative time, lower infusion volume, fewer side effects and higher surgeon satisfaction compared with patients who received oral danazol without any complications [2]. Similar to the present study, Mais et al. found that the use of vaginal danazol for 3 months before removal of endometrial polyps or hyperplasia was accompanied with a significant reduction in blood loss and no major complications [9]. In this regard, a study by Luisi et al. reported the successful vaginal administration of danazol tablets with no significant adverse effects, and the efficacy and safety of vaginal danazol was consistent with the present findings [22]. Moreover, it has been shown that endometrial thinness facilitates hysteroscopy and reduces the need for media infusion, which is accompanied with a low risk of fluid absorption and changes in serum electrolytes. Therefore, the risk of anaesthesia-related complications is also reduced. The incidence of serious complications in endoscopic surgery is high. Serum sodium levels at the end of the operation, amount of irrigation fluid and age are strong independent factors associated with this problem. Thus, these factors must be taken into account in these procedures [23].

The absence of anaesthesia-related complications in all patients in the present study could be evidence for the efficacy of both drugs in this area. It has been demonstrated that vaginal administration rather than oral administration of danazol provides the endometrium with sufficient levels of the drug, while the systemic levels of the drug and the risk of related complications are reduced [2,17]. This may justify the lack of serious side effects in patients receiving vaginal danazol in the present study. In terms of cost-effectiveness, the high cost of GnRH agonists has been cited as the restricting factor for its use in these procedures. Therefore, danazol is recommended instead. One limitation of this study was that unmarried women could not be included, as they could not use vaginal danazol.

Based on the findings of this study, vaginal danazol is preferred to GnRH agonists in patients who are candidates for hysteroscopic resection of myomas, as danazol allows for better and faster access to the uterine wall to see and perform the procedure. More prospective studies are recommended to compare the long-term outcomes of these patients.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejogrb.2015.10.021.

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